These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

REMARKS

The Status of the Claims.

Claims 1, 3, 4, 6-8, 19 and 87 are pending with entry of this amendment, claims 2, 5, 9-18 and 20-86 being cancelled and claim 87 being added herein. Claims 1, 3, 4, and 6-8 are amended herein. These amendments introduce no new matter and support is replete throughout the specification.

With respect to claims 1, 4, 6, 7 and 8, support for IL-8 can be found throughout the specification. For example, see specification at page 4, lines 14-25, at page 18, lines 1-6, at page 22, lines 6-17 and 22-24, at page 25, line 21 to page 26, line 31, at page 27, line 12 to page 28, line 4, and at page 65, lines 17-18. With respect to claim 1, support for a single interleukin-8 (IL-8) fragment can be found throughout the specification, e.g., at page 21, lines 23-28. With respect to claim 1, support for "said polypeptide comprises an ELR" motif can be found throughout the specification, e.g., at page 18, line 1-6, and at page 21, line 14 to page 22, line 17. With respect to claim 1, support for the polypeptide being no greater than about 15 amino acids in length can be found throughout the specification, e.g., at page 26, lines 26-31. With respect to claim 87, support for "wherein the polypeptide is a cyclic polypeptide" can be found throughout the specification, e.g., at page 17, lines 24-26, at page 29, line 21 to page 30, line 4, and at page 32, line 22 to page 33, line 11. Claim 3 has been amended to correct dependency.

Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

The Election/Restriction Requirement.

Pursuant to a restriction requirement made final, Applicants cancel claims 9-18 and 21-86 with entry of this amendment. Please note, however, that Applicants reserve the right to file subsequent applications claiming the canceled subject matter and that the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

Objections to the Claims

Claims 6-8 were objected for alleged informalities. Specifically the alleged informalities are that, "[c]laims 6-8 encompass non-elected inventions and require amendment to limit the invention." Action at page 3. Applicants have amended these claims to be directed to IL-8, which was the elected invention, thus, rendering the objection moot. Accordingly, Applicants request that the objection with respect to these claims be withdrawn.

35 U.S.C. §112, Second Paragraph.

Claims 6 and 7 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Action alleges that "[t]he claims are indefinite in the recitation of 70% or 90% identical to the N-terminal amino acid sequences because it is unclear what amino acid residues are encompassed in the N-terminal amino acid sequence." Action at page 7.

Claims 6 and 7 depend on amended Claim 1, which recites "[a] polypeptide comprising a single interleukin-8 (IL-8) fragment, wherein said IL-8 fragment stimulates the differentiation of fibroblasts to myofibroblasts, and wherein said fragment comprises an ELR motif, and is no greater than about 15 amino acids in length." Because claims 6 and 7 are dependent on amended claim 1, the limitations of claim 1 are incorporated into rejected claims. Claim 6 further requires that "the IL-8 fragment comprises an amino acid sequence that is at least 70% identical to an N-terminal amino acid sequence of IL-8," while claim 7 further requires that "the IL-8 fragment comprises an amino acid sequence that is at least 90% identical to an N-terminal amino acid sequence of IL-8." The specification defines "[a]n 'N-terminal' fragment [to be] a polypeptide fragment that has an amino acid sequence present in the N-terminal half of a larger polypeptide." See Specification at page 11, lines 28-29. Based on the requirements of claim 1 and claim 6, an about 15 amino acid fragment of claim 6, for example, includes at least about 11 amino acids that are the same as a corresponding sequence in the N-terminal half of IL-8. The fragment must also contain an ELR motif and be able to stimulate the differentiation of fibroblasts to myofibroblasts. Based on the requirements of claim 1 and claim 7, an about 15 amino acid fragment of claim 7, for example, includes at least about 14 amino acids that are the same as a corresponding sequence in the N-terminal half of IL-8. The fragment must also contain an ELR motif and be able to stimulate the differentiation of fibroblasts to myofibroblasts. Given the elements of independent claim 1, the

elements of the dependent claim 6 or 7 and the definition of an N-terminal fragment in the specification, it is clear what amino acid residues are encompassed by this description. As a result, claims 6 and 7 are definite and the rejection with respect to 6 and 7 should be withdrawn.

35 U.S.C. §112, First Paragraph.

Claims 1-8, 19 and 20 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Action alleges that "[t]he specification is not enabled for the instant claims because the current art does not teach that chemokines or more specifically IL-8 can stimulate the differentiation of fibroblasts to myofibroblasts" (Action at pages 4-5) and that it is unclear how a polypeptide of the invention "is not angiogenic" (Action at page 5-6) and that a fragment is not enabled that is "not 100% identical to the N-terminal amino acid sequence." (Action at page 6-7). The Examiner concluded that "[d]ue to the large quantity of experimentation necessary to demonstrate that IL-8 or variants thereof can stimulate the differentiation of fibroblasts to myofibroblast, the lack of direction/guidance present in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the contradictory state of the prior art, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope." Action at pages 6-7. Applicants traverse.

The Claims are Enabled for Polypeptides Comprising IL-8 Fragments

Claim 1 as amended recites "[a] polypeptide comprising a single interleukin-8 (IL-8) fragment, wherein said IL-8 fragment stimulates the differentiation of fibroblasts to myofibroblasts, and wherein said fragment comprises an ELR motif, and is no greater than about 15 amino acids in length." All pending claims depend upon claim 1 (claims 3, 4, 6, 7, 8, 19 and new claim 87). As the pending claims recite IL-8, this basis of the rejection must be addressed, and Applicants have done so by submitting the unsigned Declaration under 37 C.F.R. § 1.132 of Associate Professor Dr. Manuela Martins-Green, one of the co-inventors of the application. The signed Declaration of Professor Manuela Martins-Green along with her curriculum vitae will be forwarded to the Examiner as soon as these documents are received from Dr. Manuela Martins-Green.

The Declaration is submitted as evidence that the claimed invention is enabled for polypeptides comprising IL-8 and IL-8 fragments. As stated in the Declaration, "[t]his Declaration

provides evidence that IL-8 induces the differentiation of fibroblasts to myofibroblasts." Martins-Green Declaration, para 1. Dr. Martins-Green first describes immunofluorescence studies of cultured human fetal lung fibroblasts. In cultures treated with IL-8, more cells produced a marker for myofibroblast differentiation, α-SMA, then untreated cells. *Id.*, para. 2. These experiments are essentially similar to those described in the specification for cCAF at section 6 of the Example at page 69, lines 10-18. Dr. Martins-Green then points out immunoblot studies of cultured HFL-1 treated with IL-8, either a 72 amino acid form or a 77 amino acid form, which show an increased expression of α-SMA compared to untreated cells. *Id.*, para. 3. These experiments are essentially similar to those described in specification for cCAF at section 7 of the Example at page 69, line 28 to page 70, line 9. The 72 amino acid form and the 77 amino acid form of IL-8 used in the experiments described in the Declaration are disclosed in the Application at page 26 (SEQ ID NO: 5 and SEQ ID NO.: 4). Finally, Dr. Martins-Green explains that cultured HFL-1 fibroblasts treated with N-terminal fragments of IL-8 (a 6-mer and an 11-mer) show an increased expression of α-SMA compared to untreated cells. *Id.*, para. 4. The fragments used in these studies are those described in the specification at page 27 (SEQ ID NO.: 8 and SEQ ID NO.: 9) and each of these fragments contains an ELR motif. The studies described in the Declaration show that the IL-8 and IL-8 fragments can induce the differentiation from fibroblasts to myofibroblasts, as evidenced by the increased expression of α-SMA in IL-8 or IL-8 fragment treated cells.

In addition, the Examiner has indicated that cCAF experiments described in the specification "demonstrate that cCAF stimulates [the differentiation of a] fibroblast to [a] myofibroblastic phenotype." Office Action at page 5. As the IL-8 studies described in the Declaration are essentially the same as the cCAF experiments described in the specification, the IL-8 studies clearly demonstrate that IL-8 stimulates the differentiation of a fibroblast to a myofibroblastic phenotype.

Thus, the Martins-Green Declaration fully addresses the concerns raised by the Examiner. In particular, the Martins-Green Declaration establishes IL-8 and IL-8 fragments (which include an ELR motif and are no greater than about 15 amino acids in length) induce the differentiation of fibroblasts to myofibroblasts. Furthermore, the Declaration confirms, that in light of the guidance provided in the specification, one skilled in the art would have known IL-8 fragments to use. Dr. Martins-Green's Declaration thus establishes that one of skill in the art could, in fact, make and use Applicant's claimed invention. Accordingly, this basis for the rejection has

been overcome. As all pending claims relate to IL-8, Applicants submit that the pending claims fully satisfy the § 112 enablement requirement. Withdrawal of the rejection is therefore respectfully requested.

Applicants Specification Teaches How to Produce Polypeptide Variants

The Examiner's comment that "the specification is [allegedly] not enabled for fragments which are not 100% identical to the N-terminal amino acid sequence" is not the proper basis for a 35 U.S.C. § 112, first paragraph, rejection. Applicants have provided various sections in the specification describing how to make different variants and how to determine their activity. For example, see the specification at page 12, line 6 to page 15, line 12, at page 27, lines 1-11, and at page 27, line 29 to page 33, line 11. In addition, Applicants have provided definitions of the following: amino acid sequence variant, identical or percent identity (along with how to compare sequences and calculate sequence identity), conservative amino acid substitution (along with examples), polypeptide or polypeptide fragment derivative(s), and inducing the differentiation of fibroblasts to myofibroblasts. Furthermore, the polypeptides presently claimed comprise small fragments that can be readily synthesized or made using recombinant technology. These procedures are known to one of skill in the art. Applicants have provided guidance regarding these procedures in the specification, as well. For example, see the specification at the section entitled "Production of Chemokine Polypeptides" (at page 33, line 14 to page 35, line 19) and at the section entitled "Nucleic Acids, Vector and Host Cells" at page 36, line 10 to page 42, line 2.

The specification describes simple assays that can be easily carried out on the candidate variants to determine whether the fragments stimulate the differentiation of fibroblasts to myofibroblasts. For example, the specification describes that the induction of α-SMA expression is one indicator of the induction of differentiation of fibroblasts to myofibroblasts and describes how to detect the induction of α-SMA expression. See specification at page 18, lines 11-16, at page 69, line 10 to page 70, line 9, at page 73, line 28 to page 74, line 11 and Figure 4 A, B, C, D and E. Other simple assays are also described in the specification, e.g., at page 70, line 10-19, at page 71, line 7-29, at page 74, line 12 to page 76, line 11, at page 52, line 10 to page 66, line 28.

Furthermore, claim 1 requires "[a] polypeptide comprising a single interleukin-8 (IL-8) fragment, wherein said IL-8 fragment stimulates the differentiation of fibroblasts to myofibroblasts, and wherein said fragment comprises an ELR motif, and is no greater than about 15 amino acids in length." Claim 6 further requires "wherein the IL-8 fragment comprises an amino

acid sequence that is at least 70% identical to an N-terminal amino acid sequence of IL-8" and claim 7 further requires "wherein the IL-8 fragment comprises an amino acid sequence that is at least 90% identical to an N-terminal amino acid sequence of IL-8." The specification is enabled for polypeptides comprising IL-8 and IL-8 fragments, as described above. Claims 6 and 7 recite specific forms of IL-8 fragments for use in the invention, i.e., those that are at least 70% identical or at least 90% identical to an N-terminal IL-8 amino acid sequence. For example, a 15 amino acid fragment that is at least 70% identical will have at least about 11 amino acids that are the same when compared to a corresponding N-terminal IL-8 sequence. This leaves only about 4 amino acids that can vary. In the case of 90 % identical fragment, about 14 amino acids are the same as compared to a corresponding N-terminal IL-8 sequence, which leaves only about one amino acid that can vary. The specification also provides examples of both amino acid sequences and nucleotide sequences for IL-8 and IL-8 fragments. See specification at page 24 (SEQ ID NO: 3), at page 26 (SEQ ID NO: 5 and SEQ ID NO: 4), and at page 27 (SEQ ID NO: 8 and SEQ ID NO: 9). Using the above information, it is not undue experimentation to make and test all the possibilities of polypeptides that include an IL-8 fragment that is at least 70% identical or at least 90% identical to an N-terminal amino acid sequence of IL-8. These polypeptides can be chemically synthesized or recombinantly expressed according to standard methods well known to those of skill in the art or as described in the various sections of the specification described above. They can be tested for the ability to stimulate the differentiation of fibroblasts to myofibroblasts by following the specification guidance regarding suitable assays.

Thus, the specification provides sufficient guidance of the polypeptides included in the invention and teaches one of ordinary skill in the art how to make different variants and how to determine the recited activity. Accordingly, the rejection on this basis under 35 U.S.C. § 112, first paragraph, should be withdrawn.

Determination of Angiogenic Activity is Exemplified in the Specification and is Routine

The Examiner's comment that "it is [allegedly] unclear how the instant invention is not angiogenic" is also not the proper basis for a 35 U.S.C. § 112, first paragraph, rejection. Action at pages 5-6. Applicants assume that the Examiner is referring to claim 3, which recites "the polypeptide is not angiogenic." With respect to the Examiner's allegation that "it is unclear how the instant invention 'is not angiogenic,'" the Examiner quotes a section from the specification. Action,

at page 6. Specifically, the specification states that "[i]n addition to stimulating wound closure through the differentiation of myofibroblasts, cCAF may also be acting to increase the stability of new blood vessels in the granulation tissue....CXC chemokines are produced by the endothelial cells and fibroblasts of the connective tissue and promote angiogenesis....These chemokines are known to affect endothelial cell migration, but part of their role in the formation of new blood vessels may be in stimulating fibroblasts to acquire α-SMA and become the smooth muscle cells of the vasculature." Specification at page 78, lines 5-15. This part of the specification is referring to chemokines and not chemokine fragments, specifically not IL-8 fragments, which is a required limitation of the claims. Thus, this quote is not directly relevant to the pending claims. According to the specification, "[t]he term 'angiogenic' is defined...as the process of new blood vessel growth. An agent is angiogenic if treatment of a tissue with the agent results in an increase in the number of blood vessels present in the tissue, as compared to untreated tissue of the same type." Specification at page 18, lines 7-10. Determination of angiogenesis is routine to those skill in the art. The specification expressly identifies an assay that can be used to determine angiogenesis. Specifically, "angiogenesis can be assessed in the chicken chorioallantoic membrane assay." Specification at page 18, line 10. There is simply no question that the specification teaches one of ordinary skill in the art how to determine if a polypeptide is angiogenic and it is not undue experimentation to make this determination. Thus, the 35 U.S.C. § 112, first paragraph rejection with respect the pending claims should be withdrawn.

In conclusion, Applicants have provided a Declaration under 37 C.F.R. § 1.132 of Associate Professor Dr. Manuela Martins-Green that demonstrates that the claimed invention is enabled for polypeptides comprising IL-8 and IL-8 fragments. Furthermore, Applicants have pointed out various sections in the specification that provide guidance to enable one skilled in the art to make and/use the invention. Accordingly, the rejection under 35 U.S.C. § 112, first paragraph, with respect to the pending claims should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants submit that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance is respectfully requested. If the Examiner determines not to issue a Notice of Allowance, an

interview is respectfully requested prior to the issuance of another office action. In addition, if a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3502.

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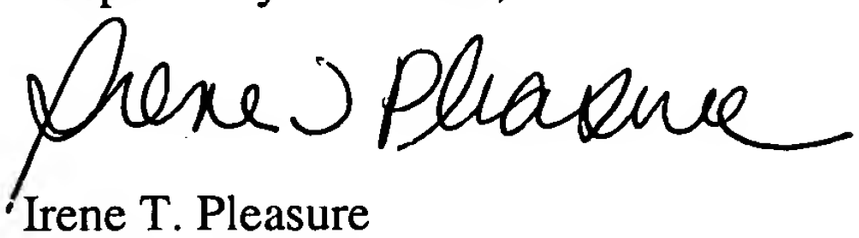
Respectfully submitted,



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APPENDIX A

"MARKED UP" CLAIMS ILLUSTRATING THE AMENDMENTS MADE TO THE CLAIMS OF 09/811,162 WITH ENTRY OF THIS AMENDMENT

1. (Amended) A polypeptide comprising a single interleukin-8 (IL-8) ~~chemokine~~ fragment, wherein said ~~chemokine~~ IL-8 fragment stimulates the differentiation of fibroblasts to myofibroblasts, and wherein said ~~polypeptide does not comprise the full-length, wild-type chemokine~~fragment comprises an ELR motif, and is no greater than about 15 amino acids in length.

3. (Amended) The polypeptide of claim ~~2~~ 1, wherein the polypeptide is not angiogenic.

4. (Amended) The polypeptide of claim ~~2~~ 1, wherein the ~~CXC chemokine~~IL-8 fragment is an N-terminal ~~CXC chemokine~~ IL-8 fragment.

6. (Amended) The polypeptide of claim ~~5~~ 1, wherein the ~~CXC chemokine~~IL-8 fragment comprises an amino acid sequence that is at least 70% identical to an N-terminal amino acid sequence of ~~chicken chemotactic and angiogenic factor (cCAF), interleukin-8 (~~IL-8~~), or melanoma growth stimulatory activity (MGSA)~~.

7. (Amended) The polypeptide of claim 6, wherein the ~~CXC chemokine~~ IL-8 fragment comprises an amino acid sequence that is at least 90% identical to an N-terminal amino acid sequence of ~~chicken chemotactic and angiogenic factor (cCAF), interleukin-8 (~~IL-8~~), or melanoma growth stimulatory activity (MGSA)~~.

8. (Amended) The polypeptide of claim 7, wherein the ~~CXC chemokine~~IL-8 fragment comprises an amino acid sequence selected from the group consisting of SEQ ID NO:8 and~~,~~ SEQ ID NO:9~~, SEQ ID NO:10, and SEQ ID NO:11~~.

87. (New) The polypeptide of claim 1, wherein the polypeptide is a cyclic polypeptide.

APPENDIX B

CLAIMS PENDING IN USSN 09/811,162 WITH ENTRY OF THIS AMENDMENT

1. A polypeptide comprising a single interleukin-8 (IL-8) fragment, wherein said IL-8 fragment stimulates the differentiation of fibroblasts to myofibroblasts, and wherein said fragment comprises an ELR motif, and is no greater than about 15 amino acids in length.

3. The polypeptide of claim 1, wherein the polypeptide is not angiogenic.

4. The polypeptide of claim 1, wherein the IL-8 fragment is an N-terminal IL-8 fragment.

6. The polypeptide of claim 1, wherein the IL-8 fragment comprises an amino acid sequence that is at least 70% identical to an N-terminal amino acid sequence of IL-8.

7. The polypeptide of claim 1, wherein the IL-8 fragment comprises an amino acid sequence that is at least 90% identical to an N-terminal amino acid sequence of IL-8.

8. The polypeptide of claim 7, wherein the IL-8 fragment comprises an amino acid sequence selected from the group consisting of SEQ ID NO:8 and SEQ ID NO:9.

19. A composition comprising the polypeptide of claim 1 and a pharmaceutically acceptable carrier.

87. The polypeptide of claim 1, wherein the polypeptide is a cyclic polypeptide.